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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/702,302	11/06/2003	Hans Maag	R0151B-REG	8005

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EXAMINER	
HABTE, KAHSAY	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 07/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/702,302	MAAG ET AL.	
	Examiner	Art Unit	
	Kahsay Habte, Ph. D.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-16 and 33-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1-3,5-16,33-43 and 47-50* is/are allowed.

6)☒ Claim(s) *44-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-3, 5-16 and 33-50 are pending in this application.

Response to Amendment

2. Applicant's amendment filed 06/22/2005 in response to the previous Office Action (03/29/2005) is acknowledged. Rejections of claims 1-3, 5-13, 15-15, 33-43 and 47-50 under 35 U.S.C. § 112, second paragraph (paragraphs 8a-8d) have been obviated.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 44-45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In claim 44, it is recited a method of treating a central nervous system disease state in a subject and in claim 45, a method of treating CNS disease state selected from psychoses, schizophrenia, manic depression, neurological disorders, memory disorders, attention deficit disorder, Parkinson's disease, amyotrophic lateral

sclerosis, Alzheimer's disease and Huntington's disease, but the specification is not enabled for such a scope.

A number of factors are relevant to whether undue experimentation would be required to practice the claimed invention, including "(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims." In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

(1). Breadth of Claims: Claims 44-45 are directed to a method of treating a central nervous system disease in a subject (claim 44) and a method of treating a central nervous system disease in a subject selected from psychoses, schizophrenia, manic depression, neurological disorders, memory disorders, attention deficit disorder, Parkinson's disease, amyotrophic lateral sclerosis, Alzheimer's disease and Huntington's disease.

a. Scope of use - The scope of use that applicants intend to claim may well be very broad. For example, in claim 44 the treatment of a central nervous system in general is claimed, but the origin and the nature of many central nervous system disorders such as Depression, Meningitis (viral, bacteria, or fungi infection), Encephalitis

(viral infection), Rett syndrome, Tinnitus, Narcolepsy, Shy-Drager syndrome, Charcot-Marie-Tooth disease, Tarsal tunnel syndrome, Psychosis, Memory loss, Mental retardation, Autism, Migraine, Tension headache, Multiple sclerosis, etc are different one from the other. The symptoms and nature of these diseases are also different one from the other. Some CNS disorders are hereditary (Charcot-Marie-Tooth disease). Many CNS disorders vary in how they affect the body and its functions. Diseases such as Cerebral palsy, and Parkinson's disease affect the movement of the patient. Diseases such as Alzheimer's disease affect the memory of the patient.

In claim 45, a method of treating Alzheimer's disease and Parkinson's disease has been recited. The central characteristic of Alzheimer's disease is the deficiency in the level of the neurotransmitter Acetylcholine that plays an important role in memory. Parkinson's disease is a neurological disorder that is also characterized by rhythmic muscle tremors, hypokinesia, and muscular rigidity. In regard to other diseases recited in claim 45, the diseases vary one from the other.

As shown above, the disorders of central nervous system (CNS) are very broad and the disorders also vary one from the other.

b. Scope of Compounds - The scope of the compounds is also broad. It is apparent that hundreds of millions of combinations of compounds can be created from the definitions, owing especially to broad scope of R^1-R^9, X, Z, p and q.

(2). Direction of Guidance: Applicants indicate that 5-HT2 selective and 5-HT6 selective ligands have been identified as potentially useful in the treatment of certain

CNS disorders such as Parkinson's disease, Huntington's disease, anxiety, depression, manic depression, psychoses, epilepsy, obsessive compulsive disorders, mood disorders, migraine etc. The amount of direction or guidance is minimal. There is no guidance for the treatment of CNS disorders that are related or affected by 5-HT2 or 5-HT6 receptors. Dosage (1-500 mg (500 fold) is generic to the disorders - same dosage for all disorders.

(3). State of Prior Art: There is no evidence of record that compounds structurally similar to these benzomorpholine derivatives recited in claim 1 as 5-HT ligands or indeed are in use for the treatment of CNS disorders recited in claim 45, let alone CNS in general recited in claim 44.

(4). Working Examples: At page 55 of the specification, an example of *in vitro* radioligand binding studies of Compound of Formula I was determined, but there is no way to convert this data into specific useful knowledge, especially in view of the difficult nature of some of these disorders. There is no link between the Ki values and the diseases recited in claims 44-45. Applicants' compounds were tested and found to be selective 5-HT-6 antagonists according to page 56.

(5). Nature of the Invention and Predictability: The invention is directed to treating CNS disorders that are related or affected by 5-HT receptors. It is well established that

"the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). CNS disorders are especially unpredictable due to their complex nature. The treatment of one type of CNS disorder could not be necessarily the same for the other type.

(6). The Relative Skill of Those in the Art: The relative skill is extremely very low. To this day, there is no magic bullet that can treat CNS disorders. Many CNS disorders have no treatment at all, e.g. autism, amnesia from alcohol blackouts.

Note that applicants' compounds are indicated as 5-HT receptors, but the claims are not limited to this. The radioligand binding test indicates that the compounds are 5-HT6 antagonists. According to a review article by Russell MG and Dias R. (Curr. Top. Med. Chem, 2002 June; 2(6):643-54), "the study for the possible role of 5-HT(6) receptor antagonists in the treatment of learning and memory disorders has stimulated significant recent work in this area", indicating that the study is at its early stage. According to the article (page 652, first paragraph), it has been concluded: "these data are open to very different interpretations which directly oppose the proposed role for 5-HT6 receptor antagonists as potential enhancers." The above statement surely contradicts the use of applicants' compounds for the treatment of CNS disorders as

recited in claims 44-45. This fundamental, unresolved contradiction shows how low is skill level in this art.

According to said article (page 650, last paragraph), it has been cited that "the current lack of full data supporting a role for 5-HT6 receptor antagonists in either behavioral inflexibility or in cognition enhancement *per se*, ... Certainly, the findings from both water maze studies are interesting and follow-up studies would be recommended." The article clearly shows that supporting data is needed for the role of 5-HT6 receptors as antagonists in behavioral inflexibility or in cognition enhancement, and that basic understanding is still lacking.

According to the article (see 648, second column last paragraph): "there are a number of potential problems regarding the behavioral findings described above. One concern is the relatively poor brain penetration ...". The cited reference in the conclusion (page 652) points out that additional studies are requires to both replicate and further investigate the functional role of the 5-HT6 receptor. In fact the authors concluded: "Indeed, to date, findings from *in vivo* studies which have attempted to shed light on 5-HT6 receptor function are ambiguous and somewhat controversial." It is clear from the article that the study is at its early stage as of June 2002 (after the filing date of the instant case). It certainly require undue experimentation to determine which central nervous system disorders are related or affected by the 5-HT6 receptors given how little is actually known about the function of 5-HT6 receptor. Despite the discrepancies noted on the article in regard to the research, applicants intend to claim the treatment of any CNS disorders that are related or affected by 5-HT6 receptor. It is up to applicants to

provide a publication that shows that their compounds can act as agonists or antagonists to treat CNS diseases that are related or affected by 5-HT receptors especially 5-HT6 receptor as indicated in the working example.

(7). The Quantity of Experimentation Necessary: Immense, because of points (1), (2) and (6).

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 46 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it

pertains, or with which it is most nearly connected, to make and/or use the invention. In claim 46, it is recited a method of treating gastrointestinal tract disorders in general, but the specification is not enabled for such a scope.

Gastrointestinal tract disorders includes diseases of the esophagus (e.g. Achalasia, gastroesophageal reflux disease), diseases of the stomach and duodenum (e.g. gastritis) and the rest of the digestive system, which includes the gastrointestinal tract itself plus three digestive organs (spleen, pancreas and liver). It also includes inflammatory bowel disease, infectious disease of the intestines, malabsorption, surgical non-neoplastic disease of the GI tract, tumors of the GI tract, Barrett's Oesophagus, Chronic Hepatitis, Cirrhosis, Coeliac Disease, Colorectal Cancer, Collagenous colitis, Colorectal Polyps, Crohn's Disease, Diverticulosis and Diverticulitis, Fatty Liver, Gastric Cancer, Gallstones, Haemochromatosis, Helicobacter pylori infection, Irritable Bowel Syndrome, Liver Failure and Liver Transplantation, Lymphocytic colitis, Microscopic colitis, Oesophageal Cancer, Pancreatitis, Peptic Ulcers, Primary Biliary Cirrhosis (PBC), Reflux Oesophagitis, Ulcerative Colitis, Viral Hepatitis, etc.

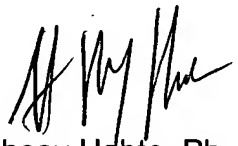
As shown by Thomas A. Godwin (GASTROINTESTINAL DISEASES, <http://edcenter.med.cornell.edu/CUMC_PathNotes/Gastrointestinal/Gastrointestinal.html>, 51 pages), the nature of the gastrointestinal disease and gastrointestinal conditions are extremely different one from the other. To this day, no one was able to treat gastrointestinal disease and gastrointestinal conditions with a single drug. Thus, the enablement rejection is proper.

Conclusion

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kahsay Habte, Ph. D. whose telephone number is (571) 272-0667. The examiner can normally be reached on M-F (9.00AM- 5:30PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Wilson (Acting SPE) can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Kahsay Habte, Ph. D.
Patent Examiner
Art Unit 1624

KH
July 7, 2005